NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

ADMINISTRATIVE GUIDELINES

FOR

MOLECULAR THERAPY CORE CENTERS

September 2002

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I. DESCRIPTION

Background

The NIDDK-supported Molecular Therapy Core Centers are part of an integrated program of cystic fibrosis (CF) and metabolic disease research. These Centers were originally established as Gene Therapy Core Centers in 1993 in response to a Congressional Appropriation. Centers provide increased, cost effective, collaboration among multidisciplinary groups of investigators at institutions with an established, comprehensive research base in gene therapy of cystic fibrosis and other genetic diseases. In 2002, the scope of the research was expanded to include related studies on gene correction and the name changed to Molecular Therapy Core Centers to reflect the expanded scope. Molecular Therapy Core Centers are intended to improve the quality and multidisciplinary nature of research on gene transfer and gene correction for cystic fibrosis and other genetic diseases by providing shared access to specialized technical resources and expertise.

General Description

The objectives of the Molecular Therapy Core Centers are to bring together investigators from relevant disciplines in a manner which will enhance and extend the effectiveness of their research. In addition to collaborations between scientists within an institution, core centers can foster interaction and collaborations between investigators at multiple institutions to promote a multifaceted approach to a common goal. The Core Center consists of several components: a single Administrative Core, several Biomedical Research Cores, and a Pilot and Feasibility Program. A core center must be an identifiable unit within a single university, medical center or a consortium of cooperative institutions, including an affiliated university. An outstanding existing program of biomedical research in the area of molecular therapies for cystic fibrosis and other genetic diseases is required. This research should be in the form of NIH-funded research projects (R01, R21), program projects (P01), specialized centers of research (P50) or other peer-reviewed research, such as that supported by the Cystic Fibrosis Foundation and the March of Dimes. This established research program must be in existence at the time of submission of a center application. Research programs outside the primary institution where the Core Center is based may utilize the core resources. The base of research projects to be served by the cores must be clearly defined and justified in the application. The research base for the Center must consist of a minimum of $1,000,000 total costs per year of peered reviewed research projects developing molecular therapies for CF. Efficient management of resources and close cooperation, communication, and collaboration among involved personnel in multiple professional disciplines are ultimate objectives of core centers.

Basic Requirements for a P30 Core Center

To be eligible for a Core Center grant, the potential applicant institution must already have a substantial base of ongoing, independently-supported, high-quality research aimed at developing

molecular therapies for cystic fibrosis and other genetic diseases. The research base for a core center is made up of investigators with individually-funded research projects who can benefit from shared resources. Core center funding will provide core facilities (shared resources), a pilot and feasibility program (new initiatives), and program enrichment activities. Each core will provide services to Core Center participants (a detailed description of Biomedical Cores begins on page 8) Except for pilot and feasibility studies, core center funds are not intended to support individual biomedical research projects other than through core usage. The major source of support for biomedical research projects associated with the Center should be derived from separately-funded projects of the participating investigators. Similarly, professional trainee stipends are not to be supported through core center funding.

A Core Center may serve a single institution or a consortium of institutions engaged in a collaborative approach to research on gene therapy of cystic fibrosis and other genetic diseases. The Core Center may be based solely at the applicant institution or at multiple institutions through subcontracts. If subcontracts are to be utilized the applicant must clearly demonstrate how a cohesive and integrated operation will be ensured and describe the advantages of this approach to performance of Core functions. The Core Center may also provide resources for funded projects at collaborating institutions which do not have a subcontractual arrangement with the parent institution. If such projects are to be included in the research base, the applicant must clearly describe and justify the reasons why it is appropriate for these projects to be included in the research base and the advantages to be derived from the collective utilization of the Core Center.

At the time of initial submission, the applicant institution or consortium of institutions must have an active program of excellence in basic and clinical biomedical research in the area of molecular therapies for cystic fibrosis and other genetic disease. The biomedical research base will be given primary consideration in the peer review process. There should be a focus on gene transfer and gene correction studies for cystic fibrosis. However, molecular therapy studies relevant to genetic endocrine, metabolic, digestive, liver, kidney, urologic and hematologic diseases may also be supported and included in the research base. Focus, relevance, interrelationships, quality, and to some extent quantity, are all considerations in judging the adequacy of the research base.

II. ADMINISTRATIVE CORE COMPONENT

Description

A Molecular Therapy Core Center must be an identifiable organizational unit within a university medical center or a consortium of cooperating institutions including the university-affiliated center. Such a Center will involve the interaction of broad and diverse elements; thus, lines of authority and approval by the appropriate institutional officials must be clearly specified. The administrative core plays a key role in the coordination and functioning of the center.

Requirements

Each applicant institution specifies a Core Center Director to be responsible for the scientific and administrative leadership of the Center. The Director should be an experienced and respected scientist with a proven track record for obtaining NIH funding. He/she must be able to coordinate, integrate, and provide guidance in the establishment of new programs in molecular therapy for cystic fibrosis and other genetic disease research. This commitment will require significant effort from the Center Director. Each Center Director is expected to commit 20% overall effort to the Center. One or more Associate Directors should be named who will be involved in the administrative, scientific, or training efforts of the center and will serve as Acting Center Director in the absence of the Director. An administrative assistant may also be proposed.

It is expected that the organization of the Administrative core should encompass a supportive structure sufficient to ensure accomplishment of the following:

(1) coordinating and integrating the Center components and activities,

(2) overseeing the solicitation, review and selection of pilot and feasibility studies,

(3) reviewing the utilization and quality of core resources

(4) interacting with the scientific and lay communities and the NIDDK in order to develop relevant goals for the Center.

The final administrative structure of the Center will be left largely to the discretion of the applicant institution (subject to review by NIH peer review mechanisms). However, NIH's experience has demonstrated that the effective development of the Center programs require close interaction between the Center director, the principal investigators, appropriate institutional administrative personnel, the staff of the awarding agency, and the members of the community in which the Center is located. Therefore, each Center applicant should establish an administrative structure which will permit the development of such interaction. Within this structure, each applicant institution must also establish a mechanism to oversee the use of funds for the proposed pilot and feasibility program. This mechanism must include the use of appropriate consultants for review from the scientific community outside the Center institution or consortium institutions. Consultants who will serve on advisory committees should not be specifically identified in the application but the process by which they will be selected should be described. These same consultants may be utilized, if desired, for review of other activities of the Center. The mechanism for reviewing the use of the pilot and feasibility funds will be considered by the initial review groups in the evaluation of the Center applications. Further details regarding this mechanism will be found below in the discussion of the pilot and feasibility program. The projects selected to receive these funds will be described by the Centers in their annual reports and will be reviewed by the NIDDK Staff for eligibility in its annual evaluation of the Center program. Funds for the Pilot and Feasibility program should be listed in the Other category in the budget of the Administrative Core. The Center grant may also include limited funds for program enrichment (i.e., seminars, etc.) which should be included in this core.

The initial base of research projects to be served by the cores must be clearly defined in the application. The process by which additional projects will be selected to utilize the core resources and by which selected projects will be prioritized must be delineated. There should be well defined criteria for designating an investigator as a Center participant. Each Center, however, is expected to formulate these definitions based on its own situation.

Although facilities available should be described for each element of the application, a more general description of overall facilities and a statement regarding institutional commitment to the Center should also be included here.

III. BIOMEDICAL RESEARCH COMPONENT

Research Base

The Core Center Grant provides a mechanism for fostering interdisciplinary cooperation within a group of established investigators conducting high quality research to develop molecular therapies for cystic fibrosis and other genetic diseases. Therefore, existence of a strong research base in this area is a fundamental requirement for and the most important aspect in the establishment of a Core Center.

Applicants should include an overview of current molecular therapy research being conducted at their institution in sufficient detail to allow reviewers to judge its extent and the interrelationship of ongoing research. There should be a substantial body of ongoing research in gene transfer and/or gene correction for cystic fibrosis. The research base may also include research to develop molecular therapy approaches for genetic endocrine, metabolic, digestive, liver, kidney, urologic and hematologic diseases. In addition, the research base should include basic studies to design, improve and test new approaches for gene transfer and gene correction. Projects at other institutions may also be included if collaborations exist with scientists at the applicant institutions. Applicants should indicate how the establishment of a Center will provide added dimensions, such as greater focus and increased cooperation, communication and collaboration.

Presentation of the research base in the application should be done in two ways: (1) by completing a Table like the one shown in Illustration III and (2) by a full description of the gene therapy related research activities at the applicant institution and any collaborating institutions. This presentation should be organized into several areas of emphasis that demonstrate the research focus of the Center. These focus areas must include a section on “Molecular therapy for CF” and a section on “Development of new molecular therapy approaches”. Additional area of emphasis relevant to the goals of the Center may be included. The research of each Center participant should be discussed and interrelationships of research being conducted by Center participants should be highlighted. Since most, if not all, of the research base will have undergone separate peer reviews, the quality of the individual funded projects is already established. The more

important aspects are: (1) interactions and interrelationships of the research efforts; (2) uses and benefits of core services; and (3) plans to develop productive collaborations among Center investigators.

There is obviously insufficient space in the application for a detailed presentation of the research base. However, significant research accomplishments should be cited and it may be helpful to include a few reprints as examples of the research conducted by Center participants as an appendix to the application. Appropriate presentation of the research base is very important since its assessment is a primary criterion in the evaluation of an application.

For renewal applications, consideration will be given to progress and accomplishments in the research base, to development of multidisciplinary, collaborative, and cooperative interrelationships, and to alteration in the original Center design in order to meet the evolving needs of the research base. This should be described in a narrative fashion and by completing a Table like the one shown in Illustration IV which documents the contribution of individual cores to the publications by the research base. Since one of the objectives of the Center is to extend research relevant to gene therapy of cystic fibrosis and other genetic diseases, new areas of research and acquisition of new funding should be highlighted.

Biomedical Research Cores

Definition: A biomedical research core is a shared facility that provides a needed service to Center investigators enabling them to conduct their funded individual research projects more efficiently and/or more effectively. Cores should be designed to furnish a group of investigators with materials, techniques, determinations, instrumentations, and/or quality control to enhance research and contribute to cost effectiveness. It is acceptable to develop a cost recovery system help defray costs to the Center. This system would charge a fee to Center participants for services provided by the Core but at a reduced rate. If such a cost recovery system is developed, a detailed charge justification must be presented and the program income section on the checklist of the PHS 398 must be completed. Participating Center members must also be informed to include such costs with their full budget justifications in their applications for individual grant support. Cores may be proposed to support any research activity of the Center, but usually fall into one of five categories: (1) provision of a technology that lends itself to automation or preparation in large batches; (2) complex instrumentation; (3) animal preparation and care; (4) clinical resources; and (5) service and training. Limited developmental research is also an appropriate function of a core facility. Such activities, however, must be directly related to enhancing the function or utility of the core. Examples of cores that could be proposed for Molecular Therapy Core Centers are listed below:

o Vector core to develop new vector designs, assist investigators with the construction of vectors, provide vectors for experimentation, and monitor vector preparations and patient samples for adventitious agents and replication competent viruses.

o DNA Delivery core to develop, distribute and test new formulations for liposome or other DNA compacting and targeting reagents for delivery of DNA.

o Animal Models core to develop, breed and maintain models for cystic fibrosis, to develop new models using knockout technology for other genetic metabolic diseases, and crossbreed mice on to new background strains to attain appropriate models for *in vivo* assessment of molecular therapies.

o Histology core to assess the efficiency of gene transfer or gene correction to particular cell types by using enzymatic histochemistry, immunohistochemistry, *in situ* hybridization or *in situ* polymerase chain reaction (PCR).

o Cell Transduction core to develop techniques for transduction or correction of cells *ex vivo* and techniques for reimplantation of modified cells. This core may also support the development of techniques for *ex vivo* selection of transduced or corrected cells.

o Electrophysiology core to measure the functional correction of CFTR in cystic fibrosis cell lines, animal studies and patient samples.

o Immunology core to analyze *in vivo* immunological responses to therapeutic genes, viral proteins and DNA delivery agents to study methods to suppress these reactions.

o Clinical core to design, conduct, monitor and provide statistical support for molecular therapy clinical trials for cystic fibrosis and other genetic diseases.

These possible cores are not listed in any particular order nor do they represent a comprehensive list of cores that could be fostered under this request for applications. Applicants are encouraged to propose other cores that address the program objectives stated above.

Justification for proposing a core: The establishment and continued support of biomedical research cores within a Center is justified on the basis of use by independently-funded Center investigators. The minimum requirement for establishing a core is significant usage by two or more investigators with independently-funded, peer-reviewed projects. While investigators holding awards from the Center pilot and feasibility program are appropriate users of the core facilities, their use does not contribute to justification for establishment or continued support of a core. Additionally, the minimum of two independently funded users does not in itself provide sufficient justification and will receive close scrutiny in review.

Personnel: A director must be named for each core. Core directors may be acknowledged experts with independently-funded research programs which will use the core services. In such cases, the percent effort on the grant is usually relatively low. A core director must contribute at least 5% effort. A core director with requisite expertise may devote a greater effort to the core and with justification could devote up to 100 percent effort. Where appropriate, an established expert in the

core activities could also be included as a consultant to the core. Technicians, etc., are allowable in accordance with the volume and type of work in the core.

Facilities, space, and special arrangements: Particularly in initial applications, the description of the physical arrangements and instrumentation for each core should be given special attention. In renewal applications, any changes should be carefully documented. Cores are encouraged, whenever possible, to enter into cooperative arrangements with established cores in other Centers or resources offering a similar type of service. However, it should be clear that the Molecular Therapy Center Cores can function independently.

Management of the core: The organization and proposed mode of operation of each core should be presented. Included should be a plan for prioritizing investigator use of the core as well as a definition of qualified users. If use by investigators outside the parent institution is proposed the mechanism by which such investigators will apply and be evaluated and selected should be detailed. The definition of qualified users should not be too narrow. Some minor core use could serve to entice established investigators in other fields into the field of molecular therapy research. Any proposed, ongoing or completed developmental efforts should be described. If the core is used to train investigators in special techniques, the mechanism for this training should be included.

Relation of core services to individual research project grants: When a Center is first established, individual investigator-initiated research project grants may include funds for a part of the services which will ultimately be available from the cores. At the time of renewal (competitive and noncompetitive) the budgets of individual research project grants must be reduced to reflect the costs supported by the Center grant. If there are charge backs, these should be detailed in the submitted budget justification and described as allowable budgetary items in the investigator's individual grants. Some mechanism should be proposed in the Center application to monitor these budgetary adjustments and to ensure that Center core users describe their relation to the Center in their individual grants.

Renewal applications: Information relative to cores in renewal applications should generally cover all of the same points as initial applications. In addition, past performance, usage and accomplishments should be described. The effect of the service provided by a core on investigator productivity and cost effectiveness should also be addressed.

Pilot and Feasibility Program

Research projects associated with a Core Center will in general be funded from other resources, such as R01, R21, P01 or P50 grants from NIH, similar project funding from other Federal agencies, or nonfederal sources. There is one exception--pilot and feasibility studies.

Definition: A Pilot and Feasibility study provides modest research support for a limited time (one to two years) to enable eligible investigators to explore the feasibility of a concept related to the

mission of the Center and generate sufficient data to pursue it through other funding mechanisms. The pilot and feasibility studies are intended to: (1) provide initial support for new investigators; (2) allow exploration of possible innovative new leads or new directions for established investigators in gene therapy and (3) stimulate investigators from other areas to lend their expertise to research in this area. Pilot and feasibility study support is not intended for large projects by established investigators which would otherwise be submitted as separate research grant applications. Pilot and feasibility funds are also not intended to support or supplement ongoing funded research of an established investigator**.**

Requirements: Each Center must contain a pilot and feasibility program with a minimum of 2 projects. A maximum of 5 projects can be requested. The funds for the pilot and feasibility program are included in the budget of the Core Center within the $750,000 direct cost cap.

Eligibility and related guidelines: Investigators eligible for pilot and feasibility funding generally fall into three categories: (1) new investigators without current or past NIH research support (R01, P01, P50) as a principal investigator (current or past support from other sources should have been modest); (2) established investigators with no previous work in molecular therapy who wish to apply their expertise to a problem in this area; and (3) established investigators who propose testing innovative ideas that represent clear departure from ongoing research interests. It is expected that the majority of the investigators will fall into the first category. All eligible investigators, however, must have faculty appointments and be independent investigators. Postdoctoral fellows or their equivalent are not eligible. Each pilot and feasibility study proposal should state clearly the justification for eligibility of the investigator under one of the above three criteria.

A proposed pilot and feasibility study should present a testable hypothesis and clearly delineate the question being asked, detail the procedures to be followed, and discuss how the data will be analyzed. It must be on a topic related to the objectives of the Core Center. Projects should be focused, since funding for these studies is modest and is limited to two years or less. Any one investigator is eligible only once for this support, unless the additional proposed pilot and feasibility study constitutes a real departure from his/her ongoing research.

Use a separate Form PHS 398 for each project, and number each project sequentially. Each pilot and feasibility project should be identified clearly by the same title as that provided in the Table of Contents. Each project should begin with an abstract, and budget pages which should be followed by information requested in Sections A through I of the instructions for Form PHS 398. It should be submitted generally using the NIH research project application format, but the research plan should be limited to five pages.

The application should clearly describe and justify the pool from which potential pilot and feasibility applications will be solicited. This can be limited to investigators at the parent institution or expanded to include investigators at institutions with well defined affiliation with the Core Center. Such an affiliation can occur either through a subcontractual relationship for support

of core resources or through inclusion of funded projects at a collaborating institution in the research base utilizing the shared resources of the Core Center. The mechanisms by which information on the availability of pilot and feasibility awards will be disseminated and by which applicants will apply and be selected for these awards must be described and will be an important element in the review of the pilot and feasibility component of the Core Center.

Initial review and management of the pilot and feasibility program: By the very nature of this program, a significant responsibility for its management will be left to the Center administration during the project periods. Each Center should include project descriptions for the Pilot and Feasibility projects they propose to fund. For new Center grant applications, the pilot and feasibility proposals are reviewed for scientific merit and eligibility by the initial review group as an example of the selectivity of their review process. These initial pilot and feasibility studies must have been reviewed by the Center in the manner proposed for review of future studies so that only those considered to be the highest quality are included in the grant application. The recommended budget for the pilot and feasibility program for the first year will be based on the review of the proposed projects. The budget for future years is recommended by the initial review group based on the quality of the proposed pilot and feasibility studies, and the proposed method for management and review (as evidenced by this set of projects). Also considered will be review group's evaluation of the future justification for continued pilot and feasibility support.

Since pilot and feasibility studies can be awarded for any period of time up to two years, studies end at various times. In addition, the studies may also be terminated by the Center administration before their approved time limit for various reasons: e.g., (1) the investigator may receive outside funding for the project; (2) the project was found not to be feasible; (3) the investigator may leave the Center institution; etc. When this occurs, the Center may make new awards for pilot and feasibility studies with the remaining funds.

While a Center's administrative framework for management of the pilot and feasibility program is basically left up to each Center (subject to NIH peer review), certain minimal requirements must be met. The program must have a director who is an established investigator in molecular therapy. There must also be a committee representing all the aspects of the Center which will assist the director in the management of the program. The major responsibilities of the director and the committee will be to:

(1) Maintain oversight and review of ongoing pilot and feasibility studies;

(2) Make recommendations regarding termination or other actions to the Center Executive Committee (or equivalent);

(3) Prepare and ensure appropriate distribution of announcements of the availability of pilot and feasibility funding;

(4) Arrange and preside over the scientific merit review of proposals. At least one

reviewer from outside the parent institution must be used for each proposal. All reviewers should assign priority scores in accordance with the NIH system. Copies of all of the proposals with written documentation of their reviews, priority scores, and final action must be retained by the Center. These records must be made available to reviewers if requested at the time of a renewal application;

(5) Maintain, insofar as is possible, a record of subsequent career events of each pilot and feasibility study recipient. This record must also be made available to reviewers at the time of the renewal application;

(6) Make recommendations to the Center Executive Committee (or equivalent) for final decisions. A record of actions by this committee must be documented and be available if requested by the initial review group.

All applicants should describe how these requirements will be met and have been met in the case of renewal applications. Also included should be an assessment of the relevancy of the proposed individual pilot and feasibility studies and of the program as a whole to research on gene therapy of cystic fibrosis and other genetic diseases and to the specific goals and objectives of the individual Center and of the Center program generally.

Review of the pilot and feasibility program in renewal applications: After the initial review of pilot and feasibility proposals as described above, all responsibility for review and funding during the remainder of the project period will reside within the Center itself. This approach provides each Center with the needed flexibility for effective and efficient management of the program. In competing renewal applications, the review of this program will be based on the past track record, the management of the program, and an assessment of overall potential needs and opportunities.

In general, a competing renewal application will include: (1) an historical overview; (2) a description of Center management of the program; (3) a description of the method for solicitation for pilot and feasibility projects and the number of respondents received for each solicitation; (4) a listing of all previous, ongoing and approved proposed pilot and feasibility studies with reports on those which were supported by the Center during the last project period; and (5) a statement relating to benefits of the program to the Center as well as the contribution of the uniqueness of the Center environment to the program. These points are detailed in the following paragraphs.

The historical overview will cover the pilot and feasibility program since the inception of the Center. This should include, in summary format, all pilot and feasibility projects ever awarded. For each project listed, the following should be included: (1) publications as a result of the studies; (2) peer-reviewed funding as a result of the studies; and (3) whether the recipient is still active in the area of gene therapy. The pilot and feasibility program director may wish to highlight certain studies or certain aspects of the past studies. Collaborations which resulted in lasting relationships, acquisition of new skills by the study recipient, or other significant outcomes should be identified. The relationship of the scope of the various studies to that of the Center

should be emphasized. Details such as back-up documentation (described earlier in relation to the arrangement of the pilot and feasibility program) should not be included, but should be available for examination by the reviewers if requested.

The description of center management of the program will present in detail the current system used to manage the pilot and feasibility program, including its integration with and relationship to the rest of the administrative structure. The use of outside consultants for review should be included in the discussion. Important features of the solicitation process should be provided including the distribution and the number of respondents.

The description of the accomplishments of the pilot and feasibility program should include a list of all NIDDK-supported pilot and feasibility studies awarded. For each pilot and feasibility project awarded during the last project period, include a brief report (1-2 pages) containing (1) the name of the investigator, degree(s), professional career status at the time awarded, and current professional career status (if known); (2) an overview of the project including its significance and salient results; (3) a list of resulting publications; and (4) peer-reviewed subsequent funding in the same or related area. The proposals should be available, if requested by the reviewers.

Funding levels for the pilot and feasibility program on renewal applications: The format for renewal of pilot and feasibility programs will depend on whether the applicant is requesting: (1) a level of effort similar to or less than that for the previous project period, or (2) an increase in the level of effort (e.g., number of projects).

If the applicant wishes to maintain the same level of effort in a renewal application, the recommendation of the initial review group will be based on the overall performance of the center's pilot and feasibility program as documented in the application. This recommendation will be based on: (1) the extent to which awarded funds were fully utilized during the previous project period; (2) awards were made to investigators who fully met the eligibility criteria for pilot and feasibility support as outlined above; (3) Center-relatedness; and (4) success of previously supported pilot and feasibility studies (e.g., publications, subsequent independent R01 or other peer-reviewed support, and/or attraction of new investigator into Center related research).

Conversely, should the applicant institution feel that an increased level of funding for the pilot and feasibility program is justified, new pilot and feasibility studies, over and above the number currently awarded, must be submitted with the competing renewal applications. These proposals would be reviewed by the initial review group in a fashion similar to the review of pilot and feasibility studies during the initial review. The initial review group would assess the new proposals, along with the overall performance of the program during the previous grant period to arrive at a recommendation for a possible increased pilot and feasibility funding level.

Research Training

Training postdoctoral fellows to conduct research in gene therapy is an associated activity of a

Center. While stipends for fellows cannot be funded from the Center, the establishment of a Center should provide an enhanced environment for research training. Just as in the case of funding for individual research projects, funding for fellowships should be sought from NIH NRSA institutional training grants (T32) and individual fellowships (F32, F33), and other sources such as the Cystic Fibrosis Foundation, other private foundations, and commercial companies.

Although no budgetary items would be included for research training, a section should be included in both initial and competing renewal applications documenting the research training program in molecular therapy its relationship to the Center, and how the presence of the Center may enhance the program.

IV. PRE-APPLICATION PROCESS

Within the limits of available funding, the Centers have been established to meet a national need. Applications will be received in response to RFAs announced in the NIH Guide for Grants and Contracts. It is strongly encouraged that potential applicants for the Centers submit a letter of intent. The letter should be sent at least one month prior to submission to allow NIDDK staff to identify potential opportunities and problems early in the development of the application. The letter of intent needs to include only: (1) names of the principal investigators and principal collaborators, (2) identification of the organization(s) involved; and (3) announcement to which the potential application is responsive. The purpose of the letter of intent is to establish communication between the potential applicant group and NIDDK staff. It is not part of the peer review material. Upon receipt of the letter, the appropriate NIDDK program director contacts the prospective principal investigator to assist in a number of areas that include scientific content and objectives, organization, and clarifications. However, applicants should not construe advice given by the NIDDK staff as assurance of favorable review. The staff will not evaluate or discuss the merit of the scientific aspects of the proposal.

V. PREPARATION OF APPLICATION

Description

Applications must be prepared using PHS 398 research grant application instructions and forms (Rev. 5/2001).
The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev 5/2001) application form (see website above) must be affixed to the bottom of the face page of the original copy of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of your application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application

form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/label-bk.pdf

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the Checklist, plus three signed photocopies, in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

At time of submission, two additional copies of the application must be sent to:

Chief, Review Branch
NIDDK, Division of Extramural Activities
Democracy 2 Room 752 MSC 5452
BETHESDA MD 20892-5452

The arrangement of materials should follow both the instructions in the PHS Form 398 application kit and the more specific guidance detailed below. Applications not in accordance with Center guidelines will be returned to the applicant by the Center for Scientific Review.

Applicants should keep in mind that the written application is the basis for the merit review. Particular attention should be given to the format of the application. Awards for Center grants will be made only for five-year project periods. Some basic information useful for preparing the application follow. Applicants may also consult with NIDDK staff concerning the technical aspects of preparing the application.

Content Order for Applications

SECTION 1: INTRODUCTION

- Face Page (398-AA) The RFA label must be affixed to the bottom of the face page and the title, AMolecular Therapy Core Centers@ and the number, DK-02-034, must be typed on line 2 and the YES box must be marked.

- Description and Key Personnel (398-BB)

- Table of Contents

- Budgets
    1. Detailed Budget for Initial Budget Period (398-DD)

2. Budget for Entire Proposed Project Period (398- EE)
3. Consolidated budget for first year of requested support (such as the one shown in Illustration I)

- o Biographical Sketches for all Center participants beginning with Center Director and Associate Director and the rest in alphabetical order (398-FF)

- o Distribution of Professional Effort on this Center application (such as the Table shown in Illustration II)

- o Summary of total current and pending support of all Center participants including percent efforts. List support related to molecular therapy for cystic fibrosis and other genetic diseases first, followed by noncenter-related research support. (Such as the Table shown in Illustration III)

- o General description of the proposed or established Center
  For Renewals: Changes from the original Center design should be highlighted

SECTION 2: ADMINISTRATIVE COMPONENT

- o Budget Page with comprehensive budgetary justifications (PHS 398 form page 4 Rev. 5/2001)

- • Qualifications of the Director and Associate Director

- o Presentation of the administrative structure

- o Relationship and lines of authority and sanction by appropriate institutional officials

- o Committee structure (include committee for the pilot and feasibility program)

- o General overall description of facilities and institutional commitment

- o Description of plans for the enrichment program

- o Other Considerations

SECTION 3: BIOMEDICAL RESEARCH COMPONENT

- o Overview of ongoing research and impact of Center on this research.
  Description of Research Base - Grouped into areas of emphasis for the

Center, two areas that must be included is Molecular therapy for cystic fibrosis and Development of Molecular Therapy Approaches

For Renewals: Progress Report including description of significant findings, new participants and new funding

- For Renewals: Publications Citing Support from this Core Center (such as the chart shown in Illustration IV)

- Biomedical research cores (present each core separately)

  Descriptive Abstract

  Budget with justifications (PHS 398 form 4 (rev. 5/2001))

  Objectives of the core

  Core function, including quality control

  Benefits from core

  Proposed developmental research or training

  Funded investigators who will use the core and proposed extent of use (such as the Table shown in Illustration V)

  For Renewal: Core Use during the last grant period (such as the Table shown in Illustration V)

- Pilot and Feasibility Program

  Composite budget with budgetary justifications for future years

  Introduction

  Director and Committee

  Management of the pilot and feasibility program

  Description of future of the pilot and feasibility program

  In initial applications include: budget and justifications, justification of eligibility as well as the scientific proposals with their justification for

core usage. For competing renewal applications, also include: overview; listing and reports of pilot and feasibility studies; and additional pilot and feasibility proposals, if applicable, as requested for an initial application.

- Research Training Program

  Description

  Other considerations

- Checklist

VI. BUDGET CONSIDERATIONS

Unless otherwise indicated in the Notice of Grant Award, allowable costs and policies governing the research grant program of the NIH will prevail. The anticipated award will be for five years. The annual direct costs requested may not exceed $750,000. Each pilot/feasibility study is limited to $50,000 per year and a two year duration of support. An exception to the $750,000 cap will apply to Core Center applications that include subcontracts. Subcontract Facilities and Administrative costs are not included in the direct cost cap of $750,000.

Budget Categories

Professional Personnel: This category may include support for salaries of key personnel within the Center who contribute to allowable activities of the Center. The salaries derived from the Center grant will depend on the effort provided and institutional salary as well as existing NIH policies; however, current NIDDK practice limits annual increments to 3 percent. The Center Director is expected to devote at least 20% of his/her efforts to the Center. The Center application should include salaries for individual principal investigators only to the extent that they provide an essential Center function. No overlap of time or effort between the Center and separately-funded projects is permitted.

Salaries of professional personnel engaged in research activities supported by pilot and feasibility funds of the Center are an allowable cost item as are salaries of professional personnel in core facilities.

Technical and Support Personnel: This may include salaries for identified positions to be filled in the Center. No overlap of time or effort between the Center and separately funded projects is permitted.

Equipment: Requests for large equipment costs must include documentation of similar equipment already available at the institution and provide a clear justification in terms of core need and

service to Center investigators. General purpose equipment needs should be included only after surveying the availability of such items within the institution.

Supplies: Consumable supplies related to the operation of the Center are allowed and include office materials, as well as scientific supplies, but should not be supplement to separately funded projects. The supply budgets of individual projects must be reduced to reflect cost savings through core usage.

Research Patient Care Costs: Research patient care costs (both in-patient and out-patient expenses) will be considered in the context of other existing institutional clinical resources. Attempts should be made by the applicant institution to utilize existing clinical facilities, such as General Clinical Research Centers and individually supported beds. Costs relating to the clinical research efforts of Center investigators may be funded through the Center, provided there is no overlap of funding. Costs already budgeted in individual projects should be appropriately reduced if such costs are to be transferred to the Center budget. The Center is not intended to be a facility for health care delivery; thus, only those patient costs directly related to research activities may be charged to the Center.

Alteration and Renovation: Funds for alteration and renovation of an existing structure to provide suitable core facilities for the Center may be made available from the grant under current PHS guidelines.

Travel: Domestic and foreign travel of project personnel directly related to the core activities of the Center is allowable. Travel of Center participants for attendance at annual Center directors meetings is allowable.

Consultants: Consultants and any associated costs (consultant fees, per diem, travel) may be included when their services are required within the Center**.**

VII. REVIEW PROCESS AND CRITERIA

Upon receipt, applications will be initially reviewed by the Center for Scientific Review (CSR) for completeness. Incomplete applications will be returned to the applicant without further consideration. Evaluation of responsiveness to the program requirements and criteria stated in this RFA is an NIDDK staff function.

Those applications which are complete and responsive will be evaluated in national competition in accordance with the criteria stated below for scientific/technical merit by an appropriate peer review group convened by the NIDDK. It is essential that the written application be in a form to be reviewed on its own merit, since no site-visit is anticipated. Following this review, the applications will be given a second level review by the National Diabetes and Digestive and Kidney Diseases Advisory Council.

The initial review group will review each application using the criteria stated below:

o Scientific excellence of the Center's research base that must have a broad and central focus in molecular therapy for CF and may extend to related research in other genetic metabolic disease. The relevance of the separately funded research to the Center objectives and the likelihood for meaningful collaboration among Center investigators must be demonstrated.

o Potential of the cores for contribution to ongoing research, including their appropriateness, impact, relevance, uniqueness, modes of operation, and suitability of facilities. Renewal applications must document the use, impact, quality control, and cost effectiveness of each core, and demonstrate progress of any developmental research in the cores. Progress will be judged in part by the publications supported by the cores. While a minimum of two users (exclusive of Pilot and Feasibility projects) are required to establish a core, a greater number of users will be considered to be more cost effective.

o Scientific and administrative abilities of the Center Director and Associate Director and their commitment and ability to devote adequate time to the effective management of the Molecular Therapy Core Center.

o The qualifications, experience, accomplishments, and commitment of the Center investigators and their inter-relatedness and collaborations.

o The Administrative organization proposed, including: coordination of ongoing research; establishment and maintenance of internal communication and cooperation among MTCC investigators; mechanisms for prioritizing usage of shares resources; mechanisms of selecting and replacing essential personnel within the Center; mechanisms for reviewing the use of and administering funds for the pilot and feasibility program, and management capabilities.

o The appropriateness of the MTCC budgets for the proposed and approved work to be done in core facilities, for pilot and feasibility studies, and for enrichment in relation to the total Center program.

o Institutional commitment to the program, including lines of accountability regarding management of the MTCC grant and a commitment to establish new positions as necessary.

o For new applications, the pilot and feasibility program is judged on the basis of: (1) scientific merit of the studies as submitted and (2) the merit of the administrative process for selecting subsequent studies. The scientific merit of the submitted pilot and feasibility studies will be evaluated for:

(1) Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(2) Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

(3) Innovation: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)? Does the PI meet one of the eligibility criteria set out in the Administrative Guidelines for pilot and feasibility studies?

(5) Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In competing renewal applications, emphasis is placed on the pilot and feasibility program as a whole, including past track record and management of the program.

o Although the MTCCs do not specifically support research training, demonstration of accomplishments and future plans related to the training of investigators necessary to conduct research in cystic fibrosis and related metabolic diseases will be considered in assessing the potential to meet Center objectives. The integration of these efforts into the overall Center, including core facilities is of particular importance. Efficient and effective use and/or planned use of the limited enrichment funds, including the contribution of these activities in enhancing the objectives of the Center will also be considered.

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

o Adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

o The reasonableness of the proposed budget to the proposed research.

O The adequacy of the proposed protection of humans, animals, or the environment, to the extent that they may be adversely affected by the project proposed in the application.

VIII. AWARD CRITERIA

Funding decisions will be based on the quality of the proposed Center as determined by peer review, overall balance in the Molecular Therapy Core Center program, and the availability of funds.

IX. EVALUATION AND REPORTING REQUIREMENTS

NIH will make information on due dates for the annual Non-competing Grant Progress Report (PHS FORM 2590) accessible electronically. Forms for PHS 2590 are available at http://grants1.nih.gov/grants/funding/2590/2590.htm For more information about electronic notification see: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-047.html

X. SPECIAL CONSIDERATIONS

While each Center will be expected to develop its own program in accordance with local talents, interests, and resources, each must be responsive to national needs to develop molecular therapy for cystic fibrosis and other genetic diseases and must be willing to work with the NIDDK and other organizations in furthering the overall goals of the Molecular Therapy Core Centers Program. In this regard, the Center Director and selected other Center participants may be invited to meet periodically with NIDDK staff and its consultants to review progress, identify emerging needs and opportunities, and plan approached for future investigations.

Within the context of these guidelines, potential applicants for Center grants are encouraged to exercise the flexibility necessary to utilize the strengths of their particular institutions in preparing a plan which will eventually cover the spectrum of required activities. While types of activities which should be included are indicated in the guidelines, specific approaches for their accomplishment are left to the individual applicant.

Because of resource limitations and in light of the size of the Center grants, it is unlikely that NIDDK will be in a position to provide hardship allowances in the event that an application for renewal of Center support is not funded.

ILLUSTRATION I
CONSOLIDATED BUDGET FOR 1st YEAR OF REQUESTED SUPPORT

Budget Category	Admin	Core A	Core B	Core C	Core D	Total
Personnel						
Consultant Costs						
Equipment						
Supplies						
Domestic Travel						
Foreign Travel						
Patient Care Costs						
Alterations and Renovations						
Other Expenses						
Contractual Costs						
Total						

ILLUSTRATION II
DISTRIBUTION OF PROFESSIONAL EFFORT (%) ON THIS APPLICATION

Participating Investigators*	Admin	Core A	Core B	Core C	P and F	Application Total	Other Support
Dr. A.	*10			10		20	50
Dr. B.		10			*10	20	40
Dr. C.	5					5	
Dr. D.			15	*10		25	55
Etc.							

***Star the percent effort (See Admin) when that individual is the core director or the principal investigator on a pilot and feasibility study. Minimum effort for Core Director is 10%. Minimum total effort for Center Director is 20%.**

ILLUSTRATION III
SUMMARY OF TOTAL CURRENT AND PENDING SUPPORT
OF ALL CENTER PARTICIPANTS

Principal Investigator Co-Investigator*	Supporting Organization and Grant Number	Title	Project Period	Current Annual Amount	Percent Effort
MOLECULAR THERAPY RESEARCH BASE **Current Support**					
Example: Doe, Joe	P01 DK00000	Novel Vectors for Gene Therapy	4/1/99-3/31/04	$500,000	40
Jones, Andrea (Doe, Joe)	K08 DK00000	Gene Therapy of Cystic Fibrosis	6/1/01-5/31/05	$75,000	50
Lane, Andrea	R01 DK00000	Gene Therapy for Gaucher Disease	7/1/01-6/30/06	$200,000	15
Pending Support					
Principal Investigator Co-Investigator	**Supporting Organization and Grant Number**	**Title**	**Project Period Requested**	**First Year Support Requested**	**Percent Effort Requested**
NON-CENTER-RELATED RESEARCH SUPPORT **Current Support** **(as above)** **Pending Support** **(as above)**					

*** If co-investigator's name is used, put principal investigator's name in parentheses below.**

ILLUSTRATION IV - FOR COMPETING RENEWALS ONLY

PUBLICATIONS CITING SUPPORT FROM THIS CORE CENTER GRANT

Contributing Cores

Core Number and P.I. Name	Publications	Core 1	Core 2	Core 3	Core 4	P & Fs
1. Brown	Brown, A.C; Jones R.C.; Smith, A.J. In vivo delivery of CFTR to monkey lung. Nature Medicine, 2000	P		S		
	Brown, A.C.; Cheng, A.G.; Anderson, J.C. Adenoviral Vectors for CF. Gene Therapy, 2001	P	S		S	
2. Cheng, A.C.	Cheng, A.C.; Meyer, G.C. Animal Models for Genetic Diseases Nature Genetics, 1999.	S	P		S	
	Smith, F.G.; Cheng, A.C.; Tissue specific Knockout of CFTR PNAS, 2000		P	S		S

***List each publication only once under the project number most significantly contributing to the work. The project most significantly contributing to the work should be signified by a AP@ (primary). All other contributing projects and cores are designated by an AS@ (secondary).**

ILLUSTRATION V
USE OF CORE FACILITIES

CORE: NAME
Determination/Services Rendered
A.
B.

Users	Funded Projects with Identifying Number	Period of Performance	Determinations/ Services	Estimated Use and Comments
1.				
2.				
3.				

EXAMPLE

CORE: Vector
Determination/Services Rendered

A.
B.
C.
D.

Users	Funded Projects with Identifying Number	Period of Performance	Determinations/ Services A B C D E	Estimated Use and Comments
1. J. F. Smith	R01 DK00000-00	3/7/97-3/7/98	X X	A. 5 per month for 12 months through 3/7/98 C. 100 per month
2. S. R. Jones	K08 DK00000-00	1/4/97-1/4/00	X	B. 40 per week through 1/4/00
3. R. G. Brown	R01 GM00000-00	9/1/01-2/1/02	X	A. 16 per week for 6 months